Letters

Balancing benefits and harms in health care

Technology to collect and share information about harms already exists

Editor—The theme issue on balancing benefits and harms in health care highlighted the need to create better systems to detect and share information about adverse events associated with newly licensed drugs or drugs used off licence or for indications not supported by evidence from clinical trials.[1 2 3]

A new project, CICERO (www.pacehealthsystems.com/cicero.html), proposes to create a global online database to record the outcomes and adverse events related to the use of investigational and newly licensed treatments. The internet offers distinct advantages to paper journals and is not geographically restricted. This is essential because we need to identify potential adverse events early after the global release of new treatments. Unlike clinical trials, internet reporting will be less selective and has the potential to detect events in untested subpopulations. It may therefore generate truer estimates of efficacy and adverse events in the general population.

Voluntary reporting systems such as the yellow card scheme in the United Kingdom have not proved successful—only 10% of serious adverse drug reactions are reported. The planned NHS information technology program may collect these data in the future, if designed properly, but this program may be dogged by data protection issues, and it is restricted to the United Kingdom. The internet solution should not be hampered by these restrictions, as it can protect patient confidentiality, conform with data protection by using explicit consent from patients, and can be globally targeted to treatments of interest—such as newly licensed drugs.

For this concept to flourish, it requires the support of the medical community; it has to be fully resourced, quality assured, peer reviewed, and free from vested interest. The technology already exists—we are limited only by our lack of imagination.

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Competing interests: None declared.

1 Pirmohamed M, Darbyshire J. Collecting and sharing information about harms. *BMJ* 3004;329:6-7. (3 July.)
2 Stricker BH, Psaty BM. Detection, verification and quantification of adverse drug reactions. *BMJ* 2004;329:44-7. (3 July.)
3 Dieppe P, Bartlett C, Davey P, Doyal L, Ebrahim S. Balancing benefits and harms: the example of non-steroidal anti-inflammatory drugs. *BMJ* 2004;329:31-4. (3 July.)

GPs need to be informed about drugs prescribed to their patients elsewhere

Editor—It is right that we consider all the possible harms of treatments.[1] A particular hazard has been drawn to the attention of the National Patient Safety Agency.[2]

General practitioners usually do not enter the names of drugs that are prescribed to their patients elsewhere (hospitals or clinical trial drugs) into their computerised patient prescribing record. Thus their approved systems are unable to flag up potential interactions. This applies to drugs such as isotretinoin.

The longer term clinical trials that continue for many years pose a particular danger. Patients may well develop comorbid conditions that need treatment by their general practitioners, who would then prescribe without appreciating the other drugs being taken. Of course the patient may be in the placebo arm, but it has to be assumed that he or she is receiving active treatment.

I am not aware of ethics committees requiring general practitioners to be notified to enter these data in a specified way on to their computer systems. I hope that systems are being modified to account for this.

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Competing interests: PR is a full time general practitioner with worries about prescribing.

1 Pirmohamed M, Darbyshire J. Collecting and sharing information about harms. *BMJ* 3004;329:6-7. (3 July.)
2 Randev P. Drug data records—a new hazard. *Prescriber* 2004;15(12). www.escriber.com/Prescriber/Features.asp?Action=View&ID=830&GroupID=36&Page=1 (accessed 12 Aug 2004).

Information about benefits and harms should be accessible to patients

Editor—I agree with Cuervo and Aronson's key point that better information is needed about all the effects of healthcare interventions, both beneficial and harmful.[1] However, the article implies that such information, suitably reported, analysed and integrated, should be used to "arm" healthcare professionals so that they can make better decisions for individuals and communities.

It is equally important to make the information available to interested patients and the general public, remembering that in most cases healthcare professionals are expert advisers but patients ultimately decide whether or not to take the treatment. Many people choose to delegate treatment decisions to doctors, but all patients who want to have a right to the information that informs their healthcare professionals. Therefore, to the authors' list of tasks for people from different disciplines we need to add "making the information available and comprehensible to patients and the public."

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Competing interests: Medicines Partnership is a Department of Health funded programme to involve patients as partners in prescribing decisions and support them in medicine taking. JMS chairs a multidisciplinary project creating a new structured source of information about medicines for patients and the public.

1 Cuervo LG, Aronson JK. The road to health care: balancing benefits and harms of interventions is essential. *BMJ* 2004;329:1-2. (3 July.)

New trial on albumin and saline should have been considered

Editor—Balancing the benefits and harms of interventions requires accurate, up to date information. Therefore, it was unfortunate that Cuervo and Aronson chose albumin for resuscitation of the critically ill as an example of an intervention which turned out to be harmful.[1]

They say that, on the basis of the Cochrane review of the subject,[2] albumin for resuscitating critically ill patients with hypovolaemia, burns, or hypoalbuminaemia probably worsens outcomes. This evidence has been superseded by the results of a recent high quality randomised controlled trial.

The saline versus albumin for fluid resuscitation (SAFE) study[3] enrolled 6997 patients (50 times the number of patients in the largest trial included in the Cochrane review) to answer the question of whether albumin is safe in the resuscitation of the critically ill. No difference was seen in 28 day mortality between patients resuscitated with

0.9% saline or albumin (relative risk 0.99; 95% confidence interval 0.91 to 1.09).

With the latest, reliable evidence we can make sensible judgments to inform our decisions on benefit and harm. On this subject, albumin is no better and no worse than 0.9% saline for fluid resuscitation of critically ill patients.

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Competing interests: None declared.

1 Cuervo LG, Aronson JK. The road to health care: balancing benefits and harms of interventions is essential. *BMJ* 2004;329:1-2. (3 July.)
2 Alderson P, Bunn F, Lefebvre C, Li WP, Li L, Roberts I, et al. Human albumin solution for resuscitation and volume expansion in critically ill patients. *Cochrane Database Syst Rev* 2002;(2):CD001208.
3 SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004;350:2247-56.

Ethical dimension was not discussed in theme issue

Editor—The interesting selection of papers in the *BMJ* on balancing harms and benefits in clinical medicine and public health all seem to make a questionable assumption. While all speak of "balancing" harms and benefits, in the arguments presented the authors assume that a purely rational judgment can be made about whether or not the true harms outweigh the true benefits.

For instance, Dieppe et al point to a dearth of evidence which causes us to misestimate the true magnitudes.[1] Greenhalgh et al point to the variety of cognitive biases which "prevent" people from making rational judgments.[2] Oakley and Johnston, with Wald, can barely conceal their annoyance at the irrational public and the devious industrial interests that try to delude them.[3]

Yet in at least some cases differences in "balancing" come about because of differences between people about what is important to them, rather than differences in estimation of probabilities and errors of logic.[4]

Some utilitarians think that everything can be reduced to a rational calculus of pleasures or pains; most of the rest of us do not. Hard choices about withdrawing drugs or licensing genetically modified crops are not hard because we are ignorant, or irrational (although we often are). They are hard because they represent conflicts of value. Failing to take account of this is the classic mistake of bureaucratic attempts at social reform from above.

A whole issue on balancing harms and benefits, without thought of the ethical dimension? An opportunity missed.

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Competing interests: None declared.

1 Dieppe P, Bartlett C, Davey P, Doyal L, Ebrahim S. Balancing benefits and harms: the example of non-steroidal anti-inflammatory drugs. *BMJ* 2004;329:31-4. (3 July.)
2 Greenhalgh T, Kostopoulou O, Harries C. Making decisions about benefits and harms of medicines. *BMJ* 2004;329:47-50. (3 July.)
3 Oakley GP, Johnston RB. Balancing benefits and harms in public health prevention programmes mandated by governments [with commentary by N J Wald]. *BMJ* 2004;329:41-4. (3 July.)
4 Chang R, ed. Incommensurability, incomparability and practical reason. Cambridge, MA: Harvard University Press, 1998.

Editor's choice was sensationalist but not true

Editor—I have for a long time thought that one of the chief obstacles to the public's understanding of medicine is the inability of the average punter to understand the concepts of probability and risk-benefit analysis that underpin most of the treatment decisions we make, and our failure as a profession to dispel that ignorance.

It was disappointing to read Smith's Editor's choice, in which he bemoans the fact that doctors seldom say to their patients: "I must warn you that the simple fact of being admitted to hospital means that you have … a one in a 100 chance of dying."[1]

We don't say it because it's not true. It may well be the case that 1% of patients admitted to hospital die, but very few patients enter hospital with a one in 100 chance of dying—for most, it's much less than that. Would Smith have us tell a young, fit patient admitted for a hernia repair that there is one chance in 100 that he or she won't come out alive? If not, which patient would he choose as the recipient of this alarming message? The patient in a road crash with multiple fractures and an aortic laceration perhaps? But in that case, of course, 1:100 would be a significant underestimate of his or her chance of dying. This is not just statistical semantics; for individual patients the 1% death rate is a complete irrelevance, and suggesting that this figure is something that they need to worry about is grossly misleading.

Such a figure may make for a headline grabbing editorial (and making a splash in the tabloids seems to have overtaken the impact factor as a measure of success for the *BMJ*), but it is not science.

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Competing interests: BB holds a conviction that the *BMJ* can no longer be considered a scientific journal.

1 Smith R. Editor's choice. Think harm always. *BMJ* 2004;329:0-g. (3 July.)

bmj.com

Summary of webchat

A webchat on the benefits and harms issue took place on 8 July 2004.[1] The editors of the theme issue began by raising several topics for discussion.

(1) Should complementary and alternative medicine have featured as much as other aspects? Would their recognition improve evidence about their benefits and harms?

(2) How will the European Trials Directive affect trials focusing on the safety of treatments?

(3) Has anyone tried to report adverse effects in a developing country?

(4) What is the role of consumers (patients) in determining an acceptable ratio of benefit to harm?

(5) Should vulnerable populations in whom drugs are not licensed such as pregnant women, children, and elderly people be considered?

The topic that dominated the webchat for most of its duration and informed whatever other ideas were raised was, however, government intervention in health care, exemplified by fortification of bread with folic acid and perhaps also vitamin B12. Participants expressed surprise that something that had been proved to be beneficial in the United States and Canada had not been implemented internationally.

The press had not taken this topic up as much as might be expected, and several participants suspected that people generally found it difficult to make up their own minds, believing what their families or the media told them. Public health interventions would be difficult to implement as a trial first because of ethical considerations. Also, when something has already been proved to be beneficial, why should a trial be necessary? The absence of knowledge of possible long term consequences to the public must be communicated.

Comparisons were made with the much debated fluoridation of drinking water, which has been rejected so far, and the legal requirement to wear seatbelts in cars and crash helmets on motorcycles, which the public seems to have adopted, although wearing a seatbelt might lead to more dangerous driving from a false sense of greater security and confidence. Seatbelts may have become widely accepted because wearing them entails an element of choice that fortifying bread with folate does not. Folate comes as a pill and is regarded as a drug, which may prejudice people. The iodisation of salt has, however, been widely accepted internationally.

Communication is key

Fashions in policy making mean that the data that inform policy vary. Academic bias may influence recommendations for or against government intervention programmes. People might not object if they knew something is being done for a good reason (salt, for example). The fact that they may just not recognise a public health measure as good might point towards a communications problem.

Maybe people who are more educated and better informed sometimes have to make decisions on behalf of those who are less well educated and informed. But the public needs to be convinced that medical professionals will do what is best, and the medical profession must do what is right but remain in a clear advisory role.

Patients should perhaps be part of research as the overlap between research outcomes and outcomes of public interest may not be complete. Communication channels are also missing for feeding

research findings into policy making. A directory of good journalists to whom doctors could confidently speak when they want to make something public might be a solution.

At the danger of repeating the same message over and over again, clear communication is important. Communication may also need to be education, rather than just information, to raise a well informed generation that participates in public debate.

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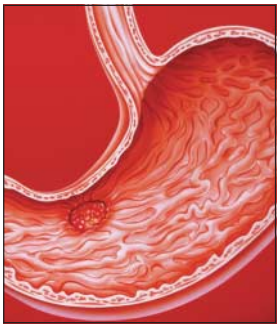
Competing interests: None declared.

1 Webchat. Balancing benefits and harms in health care. http://bmj.bmjjournals.com/cgi/content/full/329/7457/DC1 (accessed 13 Aug 2004).

Adverse drug reactions as cause of admission to hospital

Alcohol and other non-prescribed drugs may have impact on adverse drug reactions

Editor—Adverse drug reactions are an important topic for all clinicians. Pirmohamed et al report an observational study of adverse drug reactions in two large hospitals.[1] However, important clarifications are required about the method and reporting of this study. Three issues affect interpretation in ways that are important to practising clinicians, who need to be alerted to problems when prescribing.


SPL

The authors make no mention of alcohol consumption in the patients surveyed. Was alcohol consumption measured? Alcohol is an important drug that may potentiate an adverse reaction or even be an alternative cause of disease which might have been attributed to adverse drug reactions, such as gastrointestinal bleeds. This also applies to nicotine and perhaps even caffeine.

The authors do not comment on how they treated non-prescribed drugs, such as St John's wort. A systematic review in the same issue by Mills et al highlights the potential adverse reactions associated with St John's wort.[2] Other non-prescribed complementary or alternative drugs may also cause problems.

The authors say that overall, interactions accounted for 16.6% (15% to 19%) of adverse reactions. Although this overall prevalence is useful, the reader has little understanding of which drugs are particularly problematic regarding interactions. Is the problem confined to a few specific interactions with a high prevalence?

These difficulties in interpretation are illustrated by the following example. Prescribing selective serotonin reuptake inhibitors is associated with gastrointestinal bleeds, but this risk increases dramatically in conjunction with aspirin consumption.[3] Furthermore, this risk is potentiated if someone also consumes alcohol and nicotine. Clinicians may avoid prescribing potentially beneficial drugs because of concerns about an adverse reaction that may occur only in conjunction with another drug, prescribed or otherwise. Such difficulties could be overcome by presentation of data about drug interactions and mention of how non-prescription drugs were assessed by the research team.

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1 Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as a cause for admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004;329:15-9. (3 July.)
2 Mills E, Montori VM, Wu P, Gallicano K, Clarke M, Guyatt G. Interaction of St John's wort with conventional drugs: systematic review of clinical trials. *BMJ* 2004;329:27-30. (3 July.)
3 Van Walraven C, Mamdani MM, Wells PS, Williams JI. Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study *BMJ* 2001;323:655.

Not all drugs that cause adverse reactions are actually prescribed by doctors

Editor—According to the paper by Pirmohamed et al,[1] two of the drugs or drug classes implicated in adverse drug reactions are aspirin and non-steroidal anti-inflammatory drugs (NSAIDs). Both these are freely available over the counter, without the need of a prescription by a qualified doctor. This paper would have been rather stronger if it had attempted to identify whether the drugs that have been blamed had actually ever been prescribed by a doctor or had been bought over the counter. Unfortunately, the result of the publication of the paper has been a stream of rather alarmist editorials, not to mention headlines in the national media.

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Competing interests: None declared.

1 Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as a cause for admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004;329:15-9. (3 July.)

Definition of adverse drug reactions needs to include overdose

Editor—Pirmohamed et al, in assessing the burden of adverse drug reactions, excluded from their analysis any patients with either deliberate or unintentional overdose.[1] This seems inappropriate, as overdose is obviously among the risks of prescribing. The same error is inherent in the "gold standard" randomised clinical trial: it is unrealistic to expect that drugs will be used in all cases, or even most cases, precisely as intended. It is the real world experience, including misuse and abuse, which should guide our assessment of benefits and risks.

Hence, for all practical purposes, Pirhomamed et al underestimate the burden of adverse drug reactions. It would be of interest to see the results if overdoses are included. It is less clear that relapse due to non-compliance, which Pirmohamed et al also exclude, should be classified as an adverse drug reaction. However, the probability of non-compliance should be included in weighing one intervention against another, or against doing nothing.

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1 Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as a cause for admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004;329:15-9. (3 July.)

Only part of the picture was reported for aspirin

Editor—The study by Pirmohamed et al gives some insights into the problems associated with adverse drug reactions.[1] Although the statistic mainly projected is that of 6.5% (1/16) admissions due to adverse reactions, a more useful figure may be that of 107 patients who had adverse reactions that were "definitely avoidable." If we have a discussion about how these adverse reactions happened and how they could have been avoided it may help in reducing such events in future. Also useful will be a similar discussion on the reasons for the "possibly avoidable" adverse reactions.

Regarding aspirin, I don't think the study gives a correct picture. Even in the general population aspirin is a widely used drug. The study was done in a high risk population of patients admitted to hospital. In such a group we definitely expect a high intake of aspirin. Aspirin may be contributing to gastrointestinal bleeding. But a better way to assess the risk may be a study comparing similar groups of patients taking aspirin and not taking it. Therefore the value in this study does not do justice to aspirin.

It is interesting to note that five of the patients who died had renal failure as a result of medication, mainly angiotensin converting enzyme inhibitors. I would like to know whether they had some underlying renal problem and also about their duration of drug intake. It would be useful to know if the patients' renal function was tested regularly after the drug was started and whether that was of any help.

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Competing interests: None declared.

1 Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as a cause for admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004;329:15-9. (3 July.)

Admissions to ear, nose, and throat departments were not mentioned

EDITOR—Pirmohamed et al present an interesting paper on adverse drug reactions as a cause of hospital admissions,[1] but nowhere can we see any mention of problems in ear, nose, and throat medicine. Aspirin and warfarin are associated with an increased risk of epistaxis; in the case of aspirin, the relative risk of epistaxis is between 2.17 and 2.75.[2] In a recent audit in our department in the Royal Alexandra Hospital, Paisley, nearly a fifth of patients admitted as emergencies were taking aspirin or warfarin and had bleeding problems, mainly epistaxis.

We would be very surprised if no admissions to ear, nose, and throat departments were associated with adverse drug reactions during the period of the audit. Were no such departments in the two hospitals included in the study, or such admissions omitted?

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Competing interests: None declared.

1 Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as a cause for admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004;329:15-9. (3 July.)
2 Tay HL, Evans JM, McMahon AD, MacDonald TM. Aspirin, nonsteroidal anti-inflammatory drugs, and epistaxis. A regional record linkage case control study. *Ann Otol Rhinol Laryngol* 1998;107:671-4.

Authors' reply

EDITOR—The aim of our study was to elucidate the prevalence of adverse drug reactions associated with prescribed medicines. We agree with Williams and Taylor that alcohol and herbal medicines may be contributory factors but thought that our study could not accurately report on this aspect because of difficulties in verification of intake. More studies of a different design are needed in this area, and we are currently addressing the role of alcohol in warfarin related adverse drug reactions in a prospective study of 2000 patients using the AUDIT questionnaire,[1] a validated instrument to assess alcohol misuse.

With regard to interactions, we accounted for all pharmaceutical preparations being taken by patients, and the example cited—for example, selective serotonin reuptake inhibitors and aspirin—would have been classified as an interaction. Saunders questions the use of over the counter non-steroidal anti-inflammatory drugs (NSAIDS), which he says are freely available. Only oral aspirin and ibuprofen are available over the counter; the other NSAIDs are prescription only medicines. Self medication accounted for five out of the 218 aspirin related adverse reactions, while the proportion was higher for ibuprofen (nine out of 34 cases).

Laws questions our inclusion criteria, which would have included a "prescribed" overdose but excluded an intentional or accidental overdose, in accordance with a definition also put forward by the World Health Organization.[2] We agree with Joseph that avoidability is an important issue, and will be covered in greater detail in a future publication. Joseph, however, misunderstands the design of our study, which looked at patients admitted to hospital with an adverse drug reaction and not high risk patients who were in hospital. We have emphasised in the paper that our study assessed harms and did not take into account the known benefits of aspirin. In relation to angiotensin converting enzyme inhibitors, these can cause renal failure in the presence and absence of prior renal impairment, but a better evidence base is needed in relation to frequency of monitoring.[3]

Calder and MacDonald wonder about admissions caused by epistaxis. We reported only the commonest adverse drug reactions in table 4; 31 (out of 18 820) admissions were with epistaxis, of which three were caused by warfarin.

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This reply is also written by the five other authors of the paper: Andrew K Scott (consultant in care of the elderly, Wirral Hospitals NHS Trust), Thomas J Walley (professor of clinical pharmacology, Department of Pharmacology and Therapeutics, University of Liverpool), Keith Farrar (principal pharmacist, Wirral Hospitals NHS Trust), B Kevin Park (professor of pharmacology, Department of Pharmacology and Therapeutics, University of Liverpool), and Alasdair M Breckenridge (professor of clinical pharmacology, Department of Pharmacology and Therapeutics, University of Liverpool).

Competing interests: At the time of the study, AMB was chairman of the Committee on Safety of Medicines and now is chairman of the MHRA. MP is a member of the Committee on Safety of Medicines and of the subcommittee on pharmacovigilance. BKP is a member of the Committee on Safety of Medicines.

1 Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Dvelopment of Alcohol Use Disorders Identification List (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption - II. *Addiction* 1993;88:791-864.
2 World Health Organization. International drug monitoring: the role of national centres, Technical Report Series No 498. Geneva: WHO, 1972.
3 Pirmohamed M, Ferner RE. Monitoring drug treatment. *BMJ* 2003;327:1179-81. (3 July.)

Open letter to Annette King, Minister of Health, New Zealand

Intensive medicines monitoring programme is not due to be stopped

EDITOR—Herxheimer is misleading in claiming that Medsafe, the New Zealand medicines regulator, is intending to stop funding the intensive medicines monitoring programme.[1] In the past year, the ministry has provided additional funding to the New Zealand pharmacovigilance centre to intensively monitor the rollout of the meningococcal vaccine, which has been developed to deal with the meningococcal epidemic in New Zealand, using an innovative new approach distinct from the programme's methods. Medsafe, the University of Otago (where the intensive medicines monitoring programme is based), and our Medicines Adverse Reactions Committee are working together to determine the types of pharmacovigilance services that Medsafe should purchase for New Zealand. The future direction of the intensive medicines monitoring programme is part of this discussion.

New Zealand is committed to strengthening its pharmacovigilance services. In order to grow and develop, all programmes must be responsive to their environment. Since the intensive medicines monitoring programme was established in 1977, medical care and the practice of pharmacovigilance have changed dramatically. A 2003 review of the programme, conducted by its new director, identified that the programme needs to change to make it more effective, focused, and resource efficient.[2] It is hardly surprising that this review recommended change—the programme's process is extremely labour intensive as it relies heavily on paper based collection of data.

New Zealand has a proved history of innovation in the area of medicines regulation and pharmacovigilance. This was not achieved by failing to adapt to a changed environment. A final recommendation on the direction of pharmacovigilance in New Zealand is expected before Christmas.

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Competing interests: None declared.

1 Herxheimer A. Open letter to Annette King, Minister of Health, New Zealand. *BMJ* 2004;329:51. (3 July.)
2 Information for health professionals. Adverse reaction reporting and IMMP. Minutes of the medicines adverse reactions committee. www.medsafe.govt.nz/profs.htm (accessed 12 Aug 2004).

Official response is misleading

EDITOR—Matheson says that it is misleading for Herxheimer in his open letter to New Zealand's health minister to report that Medsafe, the New Zealand medicines regulator, intended to stop funding the intensive medicines monitoring programme (previous letter).[1,2] Notice was given to the University of Otago on 4 March 2004 that funding

would be withdrawn as of 30 June. Medsafe's intention was demonstrated further by the withdrawal of all usual references to the programme from the latest issue of their publication *Prescriber Update*, and from their web site. It is Matheson's letter that is misleading.

Matheson is also critical of the fact that the collection of data comes from multiple sources and is largely paper-based. He overlooks the fact that the programme has no operational alternative because of failure of Medsafe or the ministry to have prescriptions for monitored medicines recorded by a central agency. This is in spite of several promptings.

Matheson's letter implies that the methods of the intensive medicines monitoring programme have changed little from the 1970s and that the programme has not adapted to the needs of modern pharmacovigilance. The many letters of support to the director general and minister from experts around the world testify to the fact that the programme is regarded as being at the leading edge of modern pharmacovigilance.

The minister should feel embarrassed at the level of response provided on her behalf.

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Competing interests: DMC was until recently director of the intensive medicines monitoring programme.

1 Herxheimer A. Open letter to Annette King, Minister of Health, New Zealand. *BMJ* 2004;329:51. (3 July.)
2 Matheson D. Minister's response. Electronic response to Open letter to Annette King, Minister of Health, New Zealand. bmj.com 2004. http://bmj.bmjjournals.com/cgi/eletters/329/7456/51?ck=nck#65522 (accessed 13 Aug 2004).

Antidepressants and suicide

Rising prescription rate does not mean rising rate of new users

EDITOR—The figures put forward in Gunnell and Ashby's paper on suicide rates and selective serotonin reuptake inhibitor (SSRI) antidepressants, indicative of a rising prescription rate since the launch of these drugs, may be misleading, in that a rising prescription rate does not mean a rising rate of new users.[1] A formal model that translates prescriptions into patients, that we hope to submit for peer review later this year, indicates that the bulk of rising prescription rates stems not from an increasing number of new users but rather from an accumulating number of long term users of SSRIs.


BERTRAND DEMEE/PHOTONICA

This point is important in that the suicide risk with SSRIs has been linked primarily to the early weeks of treatment. If this is the case, then any increase in suicides from increasing use of SSRIs in Britain will have occurred in the years from 1989 through to 1996, after which our model shows that the number of new patients starting on SSRIs stabilises, and the contribution of SSRIs to national suicide rates should remain at some constant level, provided the effects of withdrawal on inducing suicide are not too great. This latter issue has not been studied in randomised trials, although the relative risk of a suicidal act in the post-treatment phase of the recently posted paroxetine studies in children seems to be of the order of 4.3 times greater on drug than placebo.

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Competing interests: In recent years DH has had consultancies with, been a principal investigator or clinical trialist for, been a chairman or speaker at international symposia for or been in receipt of support to attend meetings from various pharmaceutical companies (see bmj.com). He has been an expert witness for the plaintiff in seven legal actions involving SSRIs and has been consulted on a number of other attempted suicide, suicide cases, and suicide-homicide cases following antidepressant medication, in most of which he has offered the view that the treatment was not involved. He has also been an expert witness for the NHS in a series of LSD (46) and ECT (1) cases.

1 Gunnell D, Ashby D. Antidepressants and suicide: what is the balance between benefit and harm? *BMJ* 2004;329:34-8. (3 July.)

Risk of completed suicide is not the same as risk of deliberate self harm

EDITOR—I welcome Gunnell and Ashby's timely review on the risks versus benefits of selective serotonin reuptake inhibitors (SSRIs),[1] but I am not sure how much this article clears the air.

The authors take adverse "suicide related event" data reported by the Medicines and Healthcare Products Regulatory Agency (largely over-arousal, suicidal thoughts, and self harm) explicitly to mean completed suicide. Although no actual suicides occurred in the agency's data, the authors multiply an estimate of completed suicides per year in those taking antidepressants by the relative risk (incorrectly stated as "odds ratio" in table 1) of suicide related events to calculate what is claimed to be an excess number of completed suicides attributable to antidepressants. Even if both figures that they quote were correct, the final figure would be the excess of deliberate self harm in the worst case and over-arousal in the best case (but more likely a heterogeneous composite effect). Of course there is a link between deliberate self harm and suicide but it is not 1:1. The study with the longest follow up showed a 13% rate of suicide after deliberate self harm over 37 years.[2] This would translate into an excess of 30 possible cases, not 233 in men and 20 cases in women. Of course, even this smaller number would be a concern if real and not likely to be outweighed by beneficial effects in the long term (in terms of both treating the depressive syndrome and reducing complications therein).[3]

Calculating how much of the risk of a complex outcome such as suicide is attributable to one factor such as antidepressants is a difficult task, but any such calculation must be based on actual data and not estimates if one is to keep a balanced perspective on this debate. Just such a calculation has been performed for deliberate self harm with the finding that suicidal behaviour (deliberate self harm) is increased in the first one to nine days after starting an antidepressant but without major differences between individual antidepressants.[4] Clearly more research evidence is needed about the benefits and risks of SSRIs but it may be sobering to remember that less than one in 10 patients who are depressed in the community receive adequate doses of antidepressants of any type, regardless of their suicide risk.[5]

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1 Gunnell D, Ashby D. Antidepressants and suicide: what is the balance between benefit and harm? *BMJ* 2004;329:34-8.
2 Suominen K, et al. Completed suicide after a suicide attempt: a 37-year follow-up study. *Am J Psychiatry* 2004;161:563–4.
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4 Jick H, et al. Antidepressants and the risk of suicidal behaviors. *JAMA* 2004;292:338-43.
5 Suominen KH, Isometsa ET, Henriksson MM, Ostamo AI, Lonnqvist JK. Inadequate treatment for major depression both before and after attempted suicide. *Am J Psychiatry* 1998;155:1778-80.

Authors' reply

EDITOR—We agree with Aldred and Healy's suggestion that part of the recent rise in antidepressant prescribing may be due to there being a growing number of long term users of these drugs—we acknowledged this as a limitation of our model. If any adverse effects of antidepressants on suicide risk occur mainly in the first few weeks of treatment then our model will overestimate these.

Mitchell correctly identifies that one of the major assumptions we made in our model was that the risk estimates of non-fatal suicidal behaviour derived from paediatric trials could be applied to fatal suicidal behaviour in adults. We acknowledged this important limitation of our modelled "worst case scenario" in the paper. Mitchell points out the drug specific risk estimates we reported in the table are risk ratios rather than odds ratios. The odds ratios for the drug specific estimates are very similar to

the relative risks. Mitchell may have misunderstood one aspect of our model by suggesting it estimates the excess of non-fatal suicidal acts. We derived our estimates from prescribing data, the suicide rate among patients receiving antidepressants in primary care,[1] and we assumed (see above) that the relative risk of non-fatal suicidal behaviour in paediatric trials of selective serotonin reuptake inhibitors (SSRIs) is similar for suicide and all ages. If we had wished to estimate effects on non-fatal self-harm we would have used the rate among people receiving antidepressants rather than the suicide rate; as rates of non-fatal self harm are over 20 times higher than those for suicide this would result in a higher estimate.

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Competing interests: DG and DA are members of the Medical and Healthcare Products Regulatory Agency's expert working group on the safety of SSRIs, and DA is a member of the Committee on Safety of Medicines. Both act as independent advisers, receiving travel expenses and a small fee for attending meetings and reading materials in preparation for the meeting. DA has spoken on the methods of adverse drugs reactions in HIV at a scientific meeting attended by several pharmaceutical companies, and sponsored by GlaxoSmithKline. An honorarium was paid to her department.

1 Jick HSS, Dean AD, Jick H. Antidepressants and suicide. *BMJ* 1995;310:215-8.

BMJ statistical errors

Editor—Abbasi in his Editor's choice discusses a study that found statistical errors in 25% of papers published by the *BMJ* in 2001.[1] As statistical advisers to the *BMJ* we aim to improve the quality of published papers by ensuring that their conclusions are consistent with the data. To this end we hope to identify important errors that affect the interpretation of the findings, but care less about more minor errors. Any stricter policy would be impossibly time consuming. That said, we recognise that important errors do slip through from time to time, and are always keen to improve our performance.

The particular errors flagged in the paper[2] were inconsistencies between test statistics and P values. Out of 63 tests seven (11%) were wrong (for example χ^2 on 1 df = 4.2, P reported = 0.024, P actual = 0.0404). Yet in no case did the error affect the test's interpretation as to whether or not the results could have arisen by chance. This supports our belief that more extreme errors are likely to be weeded out at the review stage. The paper is disappointing in focusing on P values and by implication hypothesis testing. By contrast the *BMJ*'s policy is to present the main findings as confidence intervals where the emphasis is on estimation.[3]

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1 Editor's Choice. Do mistakes matter? *BMJ* 2004;328:0. (12 June.)
2 Garcia-Berthou E, Alcaraz C. Incongruence between test statistics and P values in medical papers. *BMC Med Res Methodol* 2004;4:13.
3 Gardner MJ, Altman DG. Confidence intervals rather than P values—estimation rather than hypothesis testing. *BMJ* 1986;292:746-50.

Government regulation is needed to prevent biased under-reporting of clinical trials

Editor—In 1996, Schering Healthcare published details of its ongoing randomised clinical trials in the *Cochrane Library*. The chief executive told me that he was doing this because industry's failure to disclose the results of its phase 3 trials could not be defended ethically or scientifically. Two years later, the chief executive of GlaxoWellcome announced his company's decision to register and seek to report all its randomised clinical trials.[1] A few years after that, the Association of the British Pharmaceutical Industry commended GlaxoWellcome's policies to its other member companies.

After GlaxoWellcome had become part of GlaxoSmithKline (GSK), I wrote to the chief executive of the new company, urging him to support the efforts of those within industry who were attempting to promulgate guidelines for good publication practice (www.gpp-guidelines.org). I received no acknowledgement, and, soon after, his company sacked one of the leaders of the initiative and closed the department she headed.

In response to accusations of biased under-reporting of research, GSK has now announced that it intends to institute policies announced seven years ago by GlaxoWellcome.[2] It would be churlish not to welcome this. But the past record of the pharmaceutical industry, and the reactions of some other companies to GSK's announcement, prompt deep scepticism that the industry will ever voluntarily implement ethical trial registration and publication policies.

Biased under-reporting of clinical trials kills patients and wastes money, and government regulation is needed to put a stop to it.[3]

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1 Sykes R. Being a modern pharmaceutical company. *BMJ* 1998;317:1172-80.
2 Gibson L. GlaxoSmithKline to publish clinical trials after US lawsuit. *BMJ* 2004;328:1513.
3 Chalmers I. In the dark. *New Scientist* 2004 March 6:9.

Access to every trial dataset is crucial

Editor—Herxheimer's pleas for access to industry's trial data[1] reminded me that I wrote to the Department of Health two or three years ago, "demanding" that all clinical trials be published either in a journal or on a company website within two years of completion. I had a less than satisfactory response which boiled down to "we can't do anything about it."

As a urologist interested in functional lower urinary tract problems (overactive bladder and possible prostatic obstruction) I have worked with many companies' "competing interests declared." In the light of this experience I approached the argument from a different perspective, that of the patients' altruism in taking part in any trial. English patients are often very committed to helping the advancement of knowledge by taking part in clinical trials and will often say "Yes, if it will help others I would like to take part." I made additional efforts to involve the Patients Association, a journal of medical ethics, and a body overseeing ethics committees in the United Kingdom, but didn't make progress.

I believe the way forward is for ethics committees to stipulate that companies must agree to publish results of any trial for which ethical approval is given. Further, ethics committees could register all trials in a single register administered by a government body, perhaps the National Institute for Clinical Excellence (NICE).

Research is important and, as Herxheimer says, it is crucial that we all have access to every trial dataset in a form that is useful, such as advised by CONSORT.

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Competing interests: None declared.

1 Herxheimer A. Open access to industry's clinically relevant data. *BMJ* 2004;329:64-5. (10 July.)